APPENDIX 1

Cancer Trials Support Unit (CTSU)

Standard Operating Procedures

Cancer Trials Support Unit (CTSU) Audit Management Program Guidelines

1.0 Introduction, Purpose and Objectives of CTSU Audit Management Program

1.1 Introduction

Although the Cooperative Group Clinical Trials System leads the world in defining the standard of cancer care and enters approximately 20, 0000 new adult patients a year on cancer treatment trials, the majority (an estimated 97-98%) of cancer patients do not enter cancer clinical trials.

In 1996, the National Cancer Institute (NCI) established an external advisory Group, the Clinical Trials Program Review Group (Armitage Committee), to review the state of the Cooperative Group Clinical Trials System and in 1997, this Committees recommendations led to the formation of the Clinical Trials Implementation Committee. The Implementation Committee made several major recommendations to the NCI to engage in a series of pilot programs to help expand the conduct of clinical trials nationally. The NCI commissioned outside experts based on discussions with the Implementation Committee to review the entire clinical trials system. Leadership of the Cooperative Group programs and other constituencies were asked to participate in those discussions. The general consensus was that the existing Cooperative Group system has certain redundancies, which if consolidated, could streamline the entire clinical trials process. The major focus of this consolidation would be to increase both patient and physician access and participation in the system.

Deliberations of the Implementation Committee led to the concept of the Cancer Trials Support Unit (CTSU). The main goals of the CTSU are as follows: 1) increase physician and patient access to adult Phase III NCI-funded clinical trials; 2) reduce regulatory and administrative burden; 3) streamline compensation methods; 4) standardize and simplify collection and reporting of Clinical Trials Data; 5) develop a web-based Informatics System and; 6) administratively assist in the pilot of a Central IRB for the NCI.

As part of the CTSU initiative to reduce regulatory and administrative burden and streamline the process for Cooperative Group member institutions, the CTSU developed a regulatory support system which includes; an Institutional Review Board (IRB) Database, a Credentials Database, a system for preparing and sponsoring Investigational New Drug Applications (IND's) and a system for Audit Management. These guidelines specifically address the purpose, objectives and process of the CTSU Audit Management Program.

1.2 Purpose and Objectives

The purpose of the CTSU Audit Management Program is to comply with Food and Drug Administration (FDA) regulations and the Cancer Therapy Evaluation Program (CTEP), NCI (NIH) guidelines for monitoring clinical trials for all CTSU enrollment as well as facilitate coordination of CTSU enrolled patient cases into the Cooperative Group audit mechanism. The objectives of the program are to assure compliance with regulatory requirements and guidelines for the conduct of clinical trials and study data validity. In addition, the Audit Management Program provides education and support regarding the research implementation to all institutional research staff.

2.0 The CTSU Audit Management Process

The CTSU will follow the audit guidelines of the Clinical Trials Monitoring Branch (CTMB), Audit Guidelines for Cooperative Groups and Clinical Community Oncology Programs (CCOP) Research Bases and CTSU (see Appendix I). The Office for Human Research Protection (OHRP), formerly the Office of Protection From Research Risks (OPRR) of the NIH, Code of Federal Regulations Title 45, Part 46, will be bases for assessing all human subject protection issues (See Appendix II).

All institutions entering patients in the CTSU will be audited at least every 36 months, but are at risk for audit during any one-year. Institutions remain at risk for audit even if their membership in the Cooperative Group is withdrawn or terminated since they have made a commitment to long-term follow-up of patients on study with provision of good quality data according to the study schedule. Affiliate Pharmacy operations are to be audited at least once during a 6-year period (i.e. every other cycle). Selection of terminated institutions for audit is at the discretion of the CTSU, and focuses on institutions that had a large accrual, particularly to important or pivotal studies and/or a large number of patients in active follow-up.

The CTSU on site audit consists of reviewing and evaluating 3 components independently with compliance to CTMB and NIH guidelines for the conduct of clinical trials. The 3 components are as follows:

1). IRB documentation and informed consent content;
2). Accountability of investigational agents and pharmacy operations; and
3). Individual patient case records

It will be vital for the CTSU Audit Coordinators to work directly with the Cooperative Group Audit Coordinator and Statistical Centers to manage the CTSU Audit Program. Section 2.1 – 2.5 will outline the process for auditing CTSU enrollment including selection of sites, scheduling sites, scheduling auditors, selecting protocol cases, data points, reporting requirements and providing follow-up information.

2.1 Selection of Sites, Scheduling of Sites, Scheduling Auditors for CTSU Patient Enrollment

CTSU Audit Management Coordinators will use the Clinical Trials Monitoring Branch (CTMB) Audit Information System (AIS) and communicate with Cooperative Group Audit Coordinators to identify which institutions are due for audit and re-audit. CTSU will determine enrollment of CTSU patients at the sites. CTSU Audit Coordinators will work with Group Audit Coordinators to augment/facilitate the Cooperative Group Audit mechanism. Depending on the number of CTSU enrolled cases and complexity of protocols, CTSU would either ask Cooperative Group auditors to audit CTSU enrolled patients or attend the Cooperative Group audit to audit the CTSU enrolled patients on site.

2.11 If ≤ 3 CTSU patients accrued at any one particular Cooperative Group member site and based on complexity of the protocol, CTSU Coordinators will ask Cooperative Group auditors to audit CTSU cases per the Cooperative Group mechanism, when the particular site is up for audit/re-audit.

2.12 If ≥ 4 CTSU patients accrued at any one particular Cooperative Group member site, CTSU auditors would augment/facilitate the Cooperative Group auditor

team for the CTSU cases. Audit dates would be coordinated with the Cooperative Group Audit Coordinators.

2.13 CTSU will enter CTSU audit date information (whether Cooperative Group auditors or CTSU auditors) into CTMB Audit Information System (AIS) at least 10 weeks prior to audit. This date would coordinate with the Cooperative Group audit date for the same site.

2.14 CTSU will provide notice of CTSU audit to the Cooperative Group to be forwarded to the audit site, at least 8 weeks in advance of the audit date.

2.2 Selection of CTSU Patient Cases for Audit

CTSU Audit Coordinators will work with Group Statistical Centers for selection of CTSU cases and particular data items to be audited. At least 10% or 3 patients (whichever is greater), of CTSU patients will be audited. Both Cooperative Group auditors and CTSU auditors will use protocol specific worksheets when auditing CTSU cases (see Appendix III for worksheets).

2.21 All cases accrued to CTSU will be eligible for selection, however the patient list will be determined from cross section of CTSU enrollment, especially multi-modality, IND, complex studies, and high accruing studies.

2.22 CTSU will send the Cooperative Group conducting the audit, the patient list for audit selection approximately 2-4 weeks in advance of the scheduled audit.

2.23 One unannounced CTSU patient case may be selected for limited review on the day of the audit (informed consent, eligibility, on study, initial treatment, first response and overall view of data quality).

2.3 Selection of Material for Review

2.31 CTSU Audit Coordinators will work with the Cooperative Group Statistical Center sponsoring the protocol, to provide copies of most or all CTSU submitted data forms to verify against the primary medical records. The submitted forms should include all data regarding eligibility and crucial outcome endpoints.

2.32 IRB approvals, annual re-approvals and all required amendment approvals for all audited protocols are reviewed.

2.33 A sample of at least 3 consent forms will be carefully reviewed for all required elements.

2.34 NCI Drug Accountability Record Forms (DARFs) for at least 3 NCI supplied agents will be reviewed where applicable. DARFs also will be cross-checked with at least 1 patient case for each of these drugs.

2.4 Audit Preparation at the Institution

2.41 The institution prepares for the audit by gathering all source documentation pertaining to the selected cases. For each selected case, the following records should be available: informed consent documents, protocol flowsheets, hospital charts, physician and research notes, outpatient and clinic records, correspondence, x-rays, scans, and other pertinent studies. The institution must flag all key documents (on-study, labs, scans and imaging studies, consent forms, etc.) to expedite the review.

2.42 For the selected protocols, the following documents should be provided: (a) the Institutional Review Board (IRB) approvals, re-approvals and amendment approvals; (b) annual reports submitted to the IRB; (c) the current version of the

protocols, including any amendments and informed consents in use at the institution.

2.43 Finally, all records regarding the disposition of investigational drugs, specifically copies of drug orders, return receipts, transfer forms, and the NCI Drug Accountability Records, must be available. The pharmacy should be alerted that the auditors will conduct an on-site inspection of investigational agent storage and records.

2.44 The Principal Investigator or designee and his/her research staff should be available throughout the audit to answer any questions and help the auditors locate necessary information in the source documents.

2.5 On-Site CTSU Audit Procedures Overview

Auditors review specific data related to research and regulatory requirements during the audit. CTSU audit checklists will be utilized to assure that all elements are reviewed. Any problems or discrepancies found are noted on the checklist, and the document must be signed by the auditors and retained by CTSU.

2.51 Review of Source Documents

Source documents should be used to independently verify study data. Source documents may include, but are not limited to, the following:

- Inpatient and outpatient medical records
- Progress notes
- Diagnostic reports (x-rays, scans, ECGS, etc.)
- Laboratory data
- Admission forms
- Study flow sheets and Protocol or Study Roadmaps that are signed and dated
- Appointment books
- Enrollment tracking sheets
- Subject diaries/calendars
- NCI Drug Accountability Record Forms (DARFS)
- Informed consents and IRB documents
- Copies of study forms (case report forms) that are used as source documentation must be signed and dated.

2.52 Assessment of Audit Findings

Each of the 3 components (IRB/Informed Consent Content, Accountability of investigational agents and Pharmacy Operations; and Individual patient case records) independently is assigned an assessment of either **Acceptable, Acceptable Needs Follow-up, or Unacceptable,** based on findings at the time of the audit. An inclusive and precise definition of what constitutes an unacceptable finding is difficult to construct. Rather than developing an inclusive quantitative definition, CTMB uses a common set of terms or examples of MAJOR and LESSER deficiencies, a common system for assessing each component of an audit, and a standard audit report format using the CTMB AIS.

2.53 Exit Interview

At the conclusion of the visit, the audit team leader conducts an exit interview(s) with the responsible investigators and all other appropriate staff. During this exit interview, the preliminary findings and any recommendations from the audit team are discussed. This interview provides opportunity for education, immediate dialogue, feedback, and clarification.

2.54 Reporting Requirements

Separate audit reporting is required for CTSU cases. A Preliminary CTSU Report of CTSU audit findings must be faxed by the audit team leader to the CTMB within one working day of completing the audit. Any major deficiencies discovered during the audit must be described in the Preliminary Report. Any findings that are suggestive of intentional misrepresentation of data and or disregard for regulatory safeguards for any of the three components of the audit must be reported to the CTMB immediately by telephone (301) 496-0510.

The audit worksheets of CTSU cases must be provided to CTSU within 2 weeks of the audit. Using audit results provided by the audit team, CTSU will enter final audit information for CTSU enrollment into the CTMB AIS within 70 working days of the date of audit. CTSU will provide an electronic copy of audit reports to the audit site and the Cooperative Group sponsoring the protocol.

2.55 Follow-up Requirements

For **each** component rated as **Acceptable Needs Follow-up** or **Unacceptable,** the institution is required to submit a written response and/or corrective action plan to the CTSU for CTSU cases. A copy of the written response/corrective action plan, along with an assessment by CTSU of the response/corrective action plan, is forwarded to CTMB within 45 days of the date the final audit report was entered into the CTMB Audit Information System. A re-audit either internal and /or on-site)is mandatory for any component rated as unacceptable